

Integrated Laboratory Systems

Diethylamine
[109-89-7]

Review of Toxicological Literature
(Update of August 1997 Review)

Prepared for

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EXECUTIVE SUMMARY

The nomination of diethylamine for carcinogenicity testing is based on high production volume, ubiquitous natural occurrence in trace amounts, and lack of sufficient chronic study data.

In 1995, the United States produced 25 million pounds (11000 Mg [metric tons]), exported 2.56 million pounds (1160 Mg), and imported 0.02 million pounds (9 Mg) of diethylamine.

Diethylamine is used for the production of the corrosion inhibitor *N,N*-diethylethanolamine (DEAE), and in the production of some pesticides and insect repellents, pharmaceuticals (e.g., the alcohol antagonist disulfiram [Antabuse], the hypnotic flurazepam [Dalmane], the anesthetic lidocaine, and the antimalarial amodiaquin), and rubber processing chemicals. It is also used in the paint, lacquer, and varnish industries.

Diethylamine was one of several primary and secondary amines detected in fresh vegetables, apples, preserves, mixed pickles, fresh and dried seafood, bread, cheese, hops, tobacco leaves, pork meat, boiled beef, stimulants and animal foodstuff. The concentrations of diethylamine were generally low, below 10 ppm (140 $\mu\text{mol/kg}$). Diethylamine has been reported to occur in the environment (e.g., the surface water in the German river Elbe II). Complete biodegradation of diethylamine takes 20 days.

Exposure to diethylamine can occur via inhalation or ingestion, through contact with the eyes, or absorption through the skin. As reported in 1984 by NIOSH, the total number of U.S. employees exposed to diethylamine was 28361 (6878 were female). Occupational exposure to diethylamine, either directly or through handling chemicals which are metabolized to diethylamine (e.g., triethylamine), occurs mostly among chemical industry workers, machinery operators, or health services workers. Low level exposure to diethylamine occurs by consumption of food and drink. Exposure to diethylamine also occurs endogenously; some drugs, such as disulfiram are metabolized to diethylamine. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a TWA threshold limit value (TLV) for diethylamine of 5 ppm (15 mg/m^3), and a TWA short-term exposure limit (STEL) of 15 ppm (45 mg/m^3). The Occupational Safety and Health Administration's (OSHA) 8-hour TWA permissible exposure limit (PEL) is 25 ppm (76 mg/m^3).

In humans, short-term inhalation exposure to diethylamine can produce respiratory tract irritation, chest pain, and breathing difficulties. Short-term dermal

exposure to liquid diethylamine can cause dermal irritation or severe burns; long-term dermal exposure to liquid diethylamine can cause chronic skin irritation. Short-term exposure of the eyes to liquid diethylamine can cause severe eye injuries, while long-term ocular exposure to diethylamine vapor may result in swelling of eyes, with foggy vision and the appearance of halos around light. People with pre-existing medical conditions may be more susceptible for these harmful effects. The estimated fatal dermal dose of diethylamine is 20 g (300 mmol).

The reaction of dietary amines with salivary nitrite may produce nitrosamines, many of which are carcinogens. However, the *in vivo* formation of nitrosodiethylamine (diethylnitrosamine) was not demonstrated in rats administered sodium nitrite and diethylamine chronically in feed.

From acute toxicity tests, the oral LD₅₀ values for diethylamine and diethylamine hydrochloride in mice and rats ranged from 500 to 1030 mg/kg (6.8 to 14.1 mmol/kg) and from 4860 to 9900 mg/kg (44.3 to 90 mmol/kg), respectively. The LD₅₀ dose for a 4-hour inhalation exposure ranged from 12000 mg/m³ (3950 ppm; 164 mmol/m³) to 17000 mg/m³ (5590 ppm; 230 mmol/m³) for rats; the lowest lethal dose by inhalation was 3000 mg/m³ (990 ppm; 41 mmol/m³) for mice. For rabbits, the dermal LD₅₀ ranged from 630 to 820 mg/kg (8.6-11 mmol/kg).

Acute exposure studies in various species by a variety of exposure routes have been conducted. Diethylamine applied acutely to the skin of rabbits caused moderate to severe skin irritation and, at high doses to occluded skin, systemic toxicity leading to death. Severe toxicity leading to death occurred in rats administered diethylamine acutely by gavage or by inhalation. In mice, intraperitoneal (i.p.) injection of diethylamine caused curare-like response (paralysis of skeletal muscles), sedation, and central nervous system depression. Temporary liver damage was observed in similarly treated rats. When administered intravenously (i.v.) to dogs, diethylamine demonstrated parasympathomimetic, sympatholytic, cardiotoxic, and vasodilator activity, and acted as a central nervous system and respiratory depressant. Severe corneal damage occurred in the eyes of rabbits following ocular application. Expiratory bradypnea indicative of upper airway irritation was present in mice evaluated during a 15-minute oronasal exposure. In rats exposed to diethylamine by inhalation for 4 hours, low concentrations caused irritation in the eyes and nostrils and tremors and poor coordination, while high doses caused convulsions, bloody discharge from the nostrils, and severe irritation to the ears and feet. Exposure to saturated vapor caused extreme

congestion of lungs, liver, kidneys, and spleen, as well as convulsions, loud rales, and corneal opacity.

Short-term and subchronic exposure to diethylamine has been evaluated in several species. In rats, oral administration of diethylamine for 2.5 months caused growth retardation and increased amounts of ascorbic acid in the liver. Also in rats, oral administration of diethylamine hydrochloride for 45 days caused inhibition of the hepatic excretory function. Mice and rats exposed to diethylamine vapor for 10 days to 6 months developed lesions of the nasal mucosa/respiratory epithelium, including squamous metaplasia and rhinitis. In rabbits, inhalation of diethylamine for 6 weeks (5 days/week) at low concentrations caused marked chronic irritation of the lungs, while exposure to higher concentrations also produced parenchymatous degeneration and, occasionally, inflammatory processes in the liver and the kidneys.

No data were found on the reproductive toxicity of diethylamine, but one study was located on the reproductive effects of diethylamine hydrochloride. In a 3-generation rat study, diethylamine hydrochloride (administered in fresh ground meat) concurrently with sodium nitrite in drinking water for life to the F₁ and F₂ generation had no effect on lifespan or reproductive performance.

Only a few studies investigating the carcinogenicity of diethylamine have been conducted. No tumors were induced in rabbits exposed by inhalation to diethylamine 5 days per week for 16 weeks. No tumors were detected in fish immersed in water containing 1/6-1/4 of the LD₅₀ for diethylamine (actual doses and duration of exposure were not provided). The incidence of liver tumors was not increased in weanling male administered a single dose of diethylamine hydrochloride by gavage and observed for 2 years. However, when diethylamine was followed immediately by treatment with sodium nitrite, a significant increase in liver tumors was observed. No liver tumors were detected in male English short-hair guinea pigs after oral (in drinking water) administration of diethylamine hydrochloride for 2.5 years, or after concurrent administration of diethylamine hydrochloride and sodium nitrite.

Diethylamine and diethylamine hydrochloride were generally found to be non-genotoxic in a limited number of prokaryotic, lower eukaryotic, and mammalian genotoxicity test systems. Diethylamine did not induce lambda prophage in *Escherichia coli*, mutations in *Salmonella typhimurium*, mutations and mitotic recombination in *Saccharomyces cerevisiae*, or unscheduled DNA synthesis in kidney cells of rats treated *in vivo*. However, diethylamine was reported to induce biochemical mutants in *Streptomyces scabies*.

Limited data were available on the immunotoxic effects of diethylamine. In guinea pigs, diethylamine administered i.p. did not demonstrate antihistaminic activity. No immunotoxicity was observed in a two-stage sensitization test with mice. Diethylamine injected i.p. caused an inhibition of cerebral and hepatic monoamine oxidase (MAO) activity in albino rats.

No data were found on chronic exposure to diethylamine.

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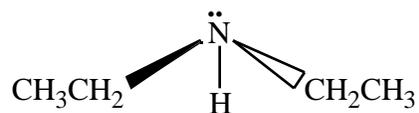
1.0 BASIS FOR NOMINATION

The nomination of diethylamine for carcinogenicity testing is based on high production volume, ubiquitous natural occurrence in trace amounts, and lack of sufficient chronic study data.

2.0 IDENTIFICATION AND CLASSIFICATION

2.1 Chemical Identification

Diethylamine (CASRN 109-89-7)



Diethylamine (C₄H₁₁N, mol. wt. = 73.14) is also called:

Ethanamine, *N*-ethyl- (9CI)
Amine, diethyl-
DEA
Diethamine
N,N-Diethylamine
N-Ethylethanamine

Diethylamine has the designation for shipping UN 1154.

This report also contains information about diethylamine hydrochloride (C₄H₁₂NCl, CASRN 660-68-9, mol wt. = 109.60).

2.2 Physical-Chemical Properties

2.2.1 Diethylamine

Property	Information	Reference
Physical State	Liquid	Budavari (1996)
Melting Point, °C	-48	Weast and Astle (1980)
Boiling Point, °C	56.3	Weast and Astle (1980)
Density at 20°C/4°C, g/mL	0.7056	Weast and Astle (1980)
Solubility:		
Water at 20°C	Miscible in all proportions	Budavari (1996)
Organic Solvents	Miscible with ethanol Soluble in diethyl ether Soluble in acetone, aliphatic and aromatic hydrocarbons, mineral oils, and stearic and oleic acids	Budavari (1996); Weast and Astle (1980) Franklin Research Center (1979); Sax (1993); Thomas (1990); all cited by BIBRA (1997)
Vapor Pressure at 20°C, mm Hg	195	NIOSH/OSHA (1981)
Odor Threshold in Air, ppm	0.14	NIOSH/OSHA (1981)
Odor Threshold in Water, ppm	0.47	Amoore et al. (1983; cited by BASF, 1995)
Odor	Strong, ammoniacal	NIOSH/OSHA (1981)
pK _a	11	Beard and Noe (1981)
pK _b	3	Beard and Noe (1981)
Partition Coefficient, log P _{ow}	0.58	BASF (1994; cited by BASF, 1995)
Flash Point, °C	-23	BASF (1994; cited by BASF, 1995)
Auto Flammability, °C	290	Elf Atochem (1988; cited by BASF, 1995)
Conversions	1 mg/L=334 ppm 1 ppm=3.04 mg/m ³	NIOSH/OSHA (1981) Ludwig (1994)

Diethylamine will attack rubber and some forms of plastics and coatings. Fires and explosions may result from contact with strong oxidizers. Fires involving diethylamine may release nitrogen oxides and carbon monoxide.

2.2.2 Diethylamine hydrochloride

Property	Information	Reference
Physical State	Solid	Budavari (1996)
Melting Point, °C	227-230	Weast and Astle (1980)
Boiling Point, °C	320-330	Weast and Astle (1980)
Density at 22°C/4°C, g/mL	1.0477	Weast and Astle (1980)
Solubility:		
Water	Soluble in water	Budavari (1996)
Organic Solvents	Soluble in ethanol, chloroform Practically insoluble in diethyl ether	Budavari (1996); Weast and Astle (1980)

3.0 COMMERCIAL PRODUCTION PROCESS

Large-scale manufacture of diethylamine is generally by high-temperature, high-pressure reaction of ammonia and an alcohol over a dehydration catalyst (method 1) or over a dehydrogenation catalyst (method 2) (Budavari, 1996; SRI Int., 1997e). Method 1 catalysts include alumina, silica-alumina, silica, titania, tungstic oxides, clays, or metal phosphates. Yields of mixed amines (primary, secondary, and tertiary) from the reaction of ammonia and alcohol in mole ratios of 2:1 to 6:1 are high (80%). The reaction product, comprising water, the alcohol, ammonia, and the amines, is treated by continuous extractions and distillations to produce the pure amines. Method 2 catalysts include silver, nickel, or copper. Byproducts include nitriles and amides. Separation of the desired product amines requires extractions and distillations (Schweizer et al., 1978). Between 3 and 4 million gallons (20-26 million pounds) of ethyl alcohol were used in 1993 to produce 20 million pounds (9000 Mg) of diethylamine (SRI Int., 1997a, e).

4.0 PRODUCTION AND IMPORT VOLUMES

U.S. producers of diethylamine include Air Products and Chemicals, Inc., Elf Atochem North America, Inc., and Hoechst Celanese Corporation (SRI Int., 1996). In the U.S., suppliers of diethylamine include Ashland Chemical Company and Elf Atochem North America, Inc.; R.S.A. Corporation is a U.S. supplier of diethylamine hydrochloride (Strum, 1997).

Since 1966, U.S. production of diethylamine has fluctuated between approximately 10 and 25 million pounds (4500-11000 Mg [metric tons]) (SRI Int., 1997a). Since 1989, export volumes have varied between approximately 1 and 3 million pounds (450-1400 Mg) (SRI Int., 1997b). In 1995, the U.S. produced 25 million pounds (11000 Mg) (SRI Int., 1997a), exported 2.56 million pounds (1160 Mg) (SRI Int., 1997b), and imported 0.02 million pounds (9 Mg) (SRI Int., 1997c) of diethylamine.

5.0 USES

Diethylamine is used in the production of the corrosion inhibitor *N,N*-diethylethanolamine (DEAE), and in the production of some pesticides and insect repellents, pharmaceuticals (e.g., the alcohol antagonist disulfiram [Antabuse], the hypnotic flurazepam [Dalmane], the anesthetic lidocaine, and the antimalarial amodiaquin), and rubber processing chemicals (SRI Int., 1997d). Diethylamine is also used in the paint, lacquer, and varnish industries (BASF, 1995).

In the U.S. in 1995, 12 million pounds (5442 Mg) of diethylamine were used to produce DEAE (54% of total consumption); 4 million pounds (1814 Mg) were used to produce pesticides and insect repellents (18% of total consumption), and 2 million pounds (907 Mg) were used in rubber processing chemicals (9% of total consumption) (SRI Int., 1997d). The amount of diethylamine used for the production of pharmaceuticals was not provided.

6.0 ENVIRONMENTAL OCCURRENCE

Diethylamine was one of several primary and secondary amines detected at low levels (generally below 10 ppm; 140 $\mu\text{mol/kg}$) in a German study analyzing fresh vegetables, preserves, mixed pickles, fish and fish products, bread, cheese, stimulants, and animal foodstuff (Neurath et al., 1977). In contrast, a subsequent German study reported that diethylamine was rarely detected among 264 foods and drinks (Pfundstein et al., 1991). No volatile secondary amines were detected in maize, kale, and English rye grass planted in Polish experimental fields (Juskiewicz and Kowalski, 1976). Less than 3 ppm (40 $\mu\text{mol/kg}$) diethylamine was found in hops, apples, tobacco leaves (Phytochemeco Database, 1996), pork meat (Patterson and Mottram, 1974), and boiled beef (Golovnya et al., 1979).

Siddiqi et al. (1992) analyzed Indian foods, and found less than 1 ppm (14 $\mu\text{mol/kg}$) diethylamine in vegetables, but higher amounts in salted tea (22 ppm; 300 $\mu\text{mol/kg}$). Low levels of diethylamine were also found in 2 of 25 types of Taiwanese fresh seafood (1 and 3 ppm; 14

and 40 µmol/kg) and 10 of 25 types of dried seafood (1-14 ppm; 14-190 µmol/kg). Frying and broiling tended to increase the concentration of diethylamine (Lin et al., 1984).

Diethylamine has been found to occur in the environment. For example, surface water of the river Elbe II (Germany) was reported to contain 9 µg/kg (120 µmol/kg) diethylamine (Neurath et al., 1977).

It takes 20 days for diethylamine to completely biodegrade; three percent of diethylamine is biodegraded after 5 days, and 41% after 10 days (Union Carbide, 1987).

7.0 HUMAN EXPOSURE

Exposure to diethylamine can occur via inhalation or ingestion, through contact with the eyes, or absorption through the skin (NIOSH/OSHA, 1981).

7.1 Occupational Exposure

As reported in 1984 by NIOSH, the total number of U.S. employees potentially exposed to diethylamine was 28361 (6878 were female) (see **Table 1** for information on exposure by industry and **Table 2** for information on exposure by occupation). Most potentially exposed workers were employed by the chemical industry (11493 workers), the petroleum and coal products industry (6593 workers), or the health services (5437 workers).

Workers who handle triethylamine, a volatile amine used as an industrial catalyst, are indirectly exposed to diethylamine, since it has been shown that triethylamine is metabolized to form diethylamine in humans (Åkesson et al., 1989). See **Section 9.2.1** for details.

Table 1. NIOSH National Occupational Exposure Survey (NOES)^a: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Agricultural Services	294	589	589
Business Services	7	28	
Chemicals and Allied Products	296	11,493	2430

Industry	Number of Plants	Number of Employees	Number of Female Employees
Fabricated Metal Products	234	937	
Health Services	215	5437	3718
Leather and Leather Products	24	48	48
Machinery, except Electrical	48	153	21
Petroleum and Coal Products	24	6593	
Primary Metal Industries	14	245	
Transportation Equipment	211	3502	72
Transportation by Air	3	94	
Trucking and Warehousing	16	242	
TOTAL	1386	29361	6878

^aNIOSH (1984)

**Table 2. NIOSH National Occupational Exposure Survey (NOES)^a:
By Occupation**

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Animal Caretakers, except Farm Workers	294	589	589
Assemblers	14	127	
Biological Technicians	21	686	300
Chemical Technicians	56	3744	1838
Clinical Laboratory Technologists and Technicians	187	4265	2839
Engineering Technicians, N.E.C.	4	41	21
Geologists and Geodesists	7	28	
Health Aides, except Nurses	24	702	468
Janitors and Cleaners	51	1848	
Laborers, except Construction Workers	18	165	91
Lathe and Turning Machine Operators	139	278	
Machine Operators, not specified	237	6827	
Miscellaneous Precision Workers, N.E.C.	3	28	

**Table 2. NIOSH National Occupational Exposure Survey (NOES)^a:
By Occupation (continued)**

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Miscellaneous Machine Operators, N.E.C.	28	1624	
Mixing and Blending Machine Operators	46	625	

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Painting and Paint Spraying Machine Operators	484	2445	163
Production Testers	3	173	
Production Inspectors, Checkers, and Examiners	5	147	
Separating, Filtering, and Clarifying Machine Operators	21	2574	386
Stock and Inventory Clerks	3	6	
Technicians, N.E.C.	18	512	183
Unspecified Mechanics and Repairers	41	82	
Vehicle Washers and Equipment Cleaners	3	94	
Welders and Cutters	21	751	
TOTAL	1728	28361	6878

Abbreviations: N.E.C. = not elsewhere classified
^aNIOSH (1984)

7.2 Dietary Exposure

Exposure to diethylamine may occur by consumption of food and drink. The mean dietary exposures to diethylamine, estimated in a 1988 German nutritional survey, were 0.22 mg/day (3.0 µmol/day) for men, and 0.16 mg/day (2.2 µmol/day) for women (Tricker et al., 1994). Based on interviews with local residents and analysis of foods in Kashmir, India, Siddiqi et al. (1992) estimated that the total average daily consumption of diethylamine by adult Indian residents was 706 µg (approximately 10 µmol).

7.3 Endogenous Exposure

In studies on the endogenous formation of secondary amines in human volunteers (Tricker et al., 1992; 1994), diethylamine was detected at a mean concentration of 0.03 µg/mL (0.4 µmol/mL) in saliva, feces and urine, and at 0.05 µg/mL (0.7 µmol/mL) (the amount varies with pH) in gastric juice. Diethylamine was not detected in the blood.

7.4 Other Exposures

Diethylamine has been detected in the urine of patients taking the drug disulfiram (tetraethylthiuram disulfide, Antabuse) to control chronic alcoholism (Neiderhiser et al., 1976). After absorption, disulfiram is rapidly reduced to its corresponding thiol, diethyl dithiocarbamate (DDTC) (Cobby et al., 1978; Eneanya et al., 1981; both cited by Faiman et al., 1984). DDTC then spontaneously decomposes to carbon disulfide and diethylamine, which is excreted in the urine (Kaslander, 1963; Faiman et al., 1978; both cited by Faiman et al., 1984). Doses of 125-500 mg disulfiram per day, or 250 mg diethylamine per day (1.68 mmol per day) on the average, are commonly taken by alcoholic patients, and maintenance therapy may continue for months or even years (PDR, 1995).

Numerous other pharmaceuticals (e.g., local anesthetics such as chlorproethazine, dibucane hydrochloride, and lidocaine; anthelmintics such as diethylcarbamazine; sedatives such as flurazepan; antibacterials such as penicillin g procaine; antimalarials such as quinacrine; and glucocorticoids such as prednisolone 21-diethylaminoacetate) contain the diethylamino moiety (Budavari, 1996, via substructure search of the CD-ROM version), and the metabolism of these pharmaceuticals also might be expected to result in diethylamine.

8.0 REGULATORY STATUS

The American Conference of Governmental Industrial Hygienists (ACGIH, 1996) has recommended a time-weighted average (TWA) threshold limit value (TLV) for diethylamine of 5 ppm (15 mg/m³) and a TWA short-term exposure limit (STEL) of 15 ppm (46 mg/m³). Occupational exposure to diethylamine is regulated as an air contaminant by the Occupational Safety and Health Administration (OSHA) under 29 CFR 1910.1000; the 8-hour TWA permissible exposure limit (PEL) is 25 ppm (76 mg/m³).

Under Department of Transportation (DOT) regulation 46 CFR 150, a number of compounds are listed as being incompatible with diethylamine. Rules for carrying incompatible

hazardous materials in bulk as cargo are prescribed. 46 CFR 153 lists the minimum requirements for transporting diethylamine, with specifications for the cargo containment system, vent height, vent, guage, fire protection system, and special requirments.

The EPA regulates diethylamine under 40 CFR 63 subpart F, National Emissions Standards for organic hazardous air pollutants from the synthetic organic chemical manufacturing industry. Section 63.106 delegates the authority for the regulation of diethylamine. 40 CFR 116 designates diethylamine as a hazardous substance which is regulated under the Federal Water Pollution Act. Under 40 CFR 117.3 and 40 CFR 302.4, the reportable quantity for release of diethylamine into water is 100 lbs. (45.4 kg). As mandated under the Toxic Substances Control Act (TSCA), 40 CFR 716.120 states that diethylamine is subject to all the provisions of part 716 and that manufacturers, importers, and processors of diethylamine are subject to reporting requirements specified in subpart A.

The use of diethylamine in adhesives used in packaging, transporting, or holding food is regulated by the Food and Drug Administration (FDA) under 21 CFR 175.105. Under 21 CFR 177.2460, poly(2,6-dimethyl-1,4-phenylene) oxide is regulated for use only as components of articles intended for repeated use. Poly(2,6-dimethyl-1,4-phenylene) oxide resins may contain diethylamine as an adjuvant substance, but diethylamine content may not exceed 0.16% by weight of the finished resin. Under 21 CFR 177.2600, diethylamine may not exceed 5% by weight of the rubber product when it is used as an activator.

9.0 TOXICOLOGICAL DATA

Summary: Based on a study using dogs, possible effects predicted in humans following administration (by any route) of a single excessive dose of diethylamine included vomiting, diarrhea, and nausea; constriction of pupils (miosis); rapid decrease in blood pressure followed by a prolonged period of decrease; an increase in pulse rate, and a decrease in pulse force; a decrease in the rate and volume of respiration; and lethargy associated with restlessness and perhaps lack of coordination. Later symptoms could include severe diarrhea and retching; miosis; a continuing decline in

blood pressure; a continuing increase in pulse rate, and a continuing decrease in pulse force until cardiovascular failure occurs; a continuing decrease in respiration; sedation; coma; and death from respiratory failure. In humans, short-term inhalation exposure to diethylamine causes respiratory tract irritation, chest pain, and breathing difficulties. Short-term exposure of bare skin to liquid diethylamine can cause dermal irritation, while short-term exposure of covered skin can cause severe burns. Long-term dermal exposure to liquid diethylamine can cause chronic skin irritation. Short-term ocular exposure to liquid diethylamine can cause severe eye injuries, while long-term ocular exposure to diethylamine vapor may result in swelling of eyes, with foggy vision and the appearance of halos around light. People with pre-existing medical conditions (e.g., impaired pulmonary function, and skin and eye disorders) may be more susceptible to these harmful effects. The estimated fatal dermal dose of diethylamine is 20 g (300 mmol).

Diethylamine was detected in the urine of healthy volunteers administered triethylamine orally. Diethylamine was also detected in the plasma and urine of alcoholic human volunteers following oral administration of the drug disulfiram and in the urine of rats treated with disulfiram.

The reaction of dietary amines with salivary nitrite may produce nitrosamines, which are carcinogens. However, the *in vivo* formation of nitrosodiethylamine (diethylnitrosamine) was not demonstrated in rats administered sodium nitrite and diethylamine chronically in the feed.

The reported oral LD₅₀ values for diethylamine and diethylamine hydrochloride in mice and rats ranged from 500 to 1030 mg/kg (6.8 to 14.1 mmol/kg) and from 4860 to 9900 mg/kg (44.3 to 90 mmol/kg), respectively. The LD₅₀ dose for a 4-hour inhalation exposure ranged from 12000 mg/m³ (3950 ppm; 164 mmol/m³) to 17000 mg/m³ (5590 ppm; 230 mmol/m³) for rats; the lowest lethal dose by inhalation was 3000 mg/m³ (990 ppm; 41 mmol/m³) for mice. For rabbits, the dermal LD₅₀ ranged from 630 to 820 mg/kg (8.6-11 mmol/kg).

Diethylamine applied acutely to the skin of rabbits caused moderate to severe skin irritation and, at high doses to occluded skin, systemic toxicity leading to death. Severe toxicity leading to death occurred in rats administered diethylamine acutely by gavage or by inhalation. In mice, i.p. injection of diethylamine caused curare-like response (paralysis of skeletal muscles), sedation, and central nervous system depression. Temporary liver damage was observed in similarly treated rats. When administered i.v. to dogs, diethylamine demonstrated parasympathomimetic, sympatholytic, cardiotoxic, and vasodilator activity, and acted as a central nervous

system and respiratory depressant. Severe corneal damage occurred in the eyes of rabbits following ocular application. Expiratory bradypnea indicative of upper airway irritation was present in mice evaluated during a 15-minute oronasal exposure. In rats exposed to diethylamine by inhalation for 4 hours, low concentrations caused irritation in the eyes and nostrils and tremors and poor coordination, while high doses caused convulsions, bloody discharge from the nostrils, and severe irritation to the ears and feet. Exposure to saturated vapor caused extreme congestion of lungs, liver, kidneys, and spleen, as well as convulsions, loud rales, and corneal opacity.

In rats, oral administration of diethylamine for 2.5 months caused growth retardation and increased amounts of ascorbic acid in the liver. Also in rats, oral administration of diethylamine hydrochloride for 45 days caused inhibition of the hepatic excretory function. Mice and rats exposed to diethylamine vapor for 10 days to 6 months developed lesions of the nasal mucosa/respiratory epithelium, including squamous metaplasia and rhinitis. In rabbits, inhalation of diethylamine for 6 weeks (5 days/week) at low concentrations caused marked chronic irritation of the lungs, while exposure to higher concentrations also produced parenchymatous degeneration and, occasionally, inflammatory processes in the liver and the kidneys.

In a 3-generation reproductive toxicity and teratogenicity rat study, diethylamine hydrochloride (administered in fresh ground meat) concurrently with sodium nitrite in drinking water for life to the F₁ and F₂ generation had no effect on lifespan or reproductive performance.

No tumors were induced in rabbits exposed by inhalation to diethylamine 5 days per week for 16 weeks. No tumors were detected in fish immersed in water containing 1/6-1/4 of the LD₅₀ for diethylamine (actual doses and duration of exposure were not provided). The incidence of liver tumors was not increased in weanling male administered a single dose of diethylamine hydrochloride by gavage and observed for 2 years. However, when diethylamine was followed immediately by treatment with sodium nitrite, a significant increase in liver tumors was observed. No liver tumors were detected in male English short-hair guinea pigs after oral (in drinking water) administration of diethylamine hydrochloride for 2.5 years, or after concurrent administration of diethylamine hydrochloride and sodium nitrite.

Diethylamine and diethylamine hydrochloride were generally found to be non-genotoxic in a limited number of prokaryotic, lower eukaryotic, and mammalian test systems. Diethylamine did not induce lambda prophage in *Escherichia coli*, mutations in *Salmonella typhimurium*, mutations and mitotic recombination in *Saccharomyces cerevisiae*, or unscheduled DNA synthesis in kidney cells of rats treated *in vivo*.

However, diethylamine was reported to induce biochemical mutants in *Streptomyces scabies*.

In guinea pigs, diethylamine administered i.p. did not demonstrate antihistaminic activity. No immunotoxicity was observed in a two-stage sensitization test with mice. Diethylamine caused an inhibition of cerebral and hepatic monoamine oxidase (MAO) activity in albino rats injected i.p.

Structure-activity relationships have not been reviewed.

9.1 Human Data

9.1.1 Predicted Effects

Based on a study that investigated the toxicity of diethylamine administered intravenously (i.v.) to dogs, Union Carbide (1955) predicted the possible effects in humans following administration (by any route) of a single excessive dose of diethylamine. Early symptoms were predicted to include vomiting, diarrhea, and nausea; constriction of pupils (miosis); rapid decrease in blood pressure followed by a prolonged period of decrease; an increase in pulse rate, and a decrease in pulse force; a decrease in the rate and volume of respiration; and lethargy associated with restlessness and perhaps lack of coordination. Later symptoms could include severe diarrhea and retching; miosis; a continuing decline in blood pressure; a continuing increase in pulse rate, and a continuing decrease in pulse force until cardiovascular failure occurs; a continuing decrease in respiration; sedation; coma; and death from respiratory failure.

Short-term inhalation exposure of humans to diethylamine causes respiratory tract irritation, chest pain, and breathing difficulties (NIOSH/OSHA, 1981). Short-term exposure of bare skin to liquid diethylamine can cause dermal irritation, while short-term exposure of covered skin (including skin covered by clothing wet with diethylamine) can cause severe burns. Long-term dermal exposure to liquid diethylamine can cause chronic skin irritation. Short-term ocular exposure to liquid diethylamine can cause severe eye injuries, while long-term ocular exposure to diethylamine vapor may result in the swelling of eyes, with foggy vision and the appearance of

halos around lights. People with pre-existing medical conditions (e.g., impaired pulmonary function and skin and eye disorders) may be more susceptible to the adverse effects of diethylamine.

The estimated fatal dermal dose of diethylamine for a human is 20 g (300 mmol) (Dreisbach and Robertson, 1987).

9.1.2 Experimental Studies

An oral dose (amount not provided) of diethylamine hydrochloride was well tolerated by test subjects (Rechenberger, 1940; cited by BASF, 1995). Within 24 hours, 86% of the dose was excreted. No other details were reported.

In four test subjects exposed to 0.047 and 0.028 mL/m³ (0.033 and 0.020 mg/m³; 0.011 and 0.0066 ppm) diethylamine in the air, the light sensitivity of the eyes was reduced (Kosiborod, 1968; cited by BASF, 1995). Following exposure to 0.021 mL/m³ (0.015 mg/m³; 0.0049 ppm) in the air, electroencephalogram readings indicated a decrease in brain waves. No symptoms were reported following exposure to 0.015 mL/m³ (0.010 mg/m³; 0.0033 ppm) in the air.

Five volunteers exposed to diethylamine concentrations ranging from 0 to 12 ppm (average concentration = 10 ppm [30 mg/m³, 0.41 mmol/m³]) in the air over a one-hour period experienced eye and nasal irritation (Lundqvist et al., 1992; cited by BIBRA, 1997).

Subjects exposed to 25 ppm (76 mg/m³; 1.0 mmol/m³) diethylamine for 15 minutes in an inhalation booth did not experience nasal irritation or changes in breathing resistance (Lundqvist et al., 1992; cited by BASF, 1995). Following exposure to 30 ppm (91 mg/m³; 1.2 mmol/m³) for 1 hour, subjects experienced nose and eye irritation and a change in the sense of smell.

9.1.3 Case Reports

In one case after liquid diethylamine was accidentally splashed into the eyes, immediate, intense pain resulted (NIOSH/OSHA, 1981). Although the eyes were immediately flushed and treated, corneal damage and some permanent visual impairment occurred.

Occupational exposure to diethylamine vapors (concentrations not reported) caused corneal edema as well as eye irritation (Patty, 1963; cited by NIOSH/OSHA, 1981).

One case of double vision was reported in an employee handling diethylamine, but further details were not provided (Munn, 1967; cited by BASF, 1995). In an unrelated report by Grant (1986; cited by BASF, 1995), double vision from occupational exposure to diethylamine was recorded. The symptoms became apparent several hours after exposure. When workers were occupationally exposed to low concentrations (not provided), the symptoms disappeared after 1 day. At higher diethylamine exposure concentrations (not provided), the symptoms persisted for numerous days.

In an occupational health evaluation of workers at the Koppers Coating and Resins Plant in Irving, Texas, 26 employees (23 men, 3 women) were medically examined (Koppers Co., 1982). The chemical inventory at the plant included diethylamine and 38 other compounds that were considered high volume materials (greater than 1000 lb or 1000 gal per year). It was not specified if the compounds were produced at the plant or were purchased elsewhere. Medical examination of the workers did not reveal unusually high incidences of diseases of the central nervous system, kidney, liver, blood-forming organs, or skin. Although pulmonary function tests revealed some abnormalities in the workers, Koppers Co. stated that the tests were “not technically adequate and [that] the numbers presented [were] probably misleading.”

9.2 General Toxicology

9.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

9.2.1.1 Diethylamine as Metabolite of Triethylamine and Triethylamine-*N*-oxide

The disposition of triethylamine (TEA), and its metabolite triethylamine-*N*-oxide (TEAO), were evaluated in healthy male volunteers. The compounds were administered both orally (TEA at a dose of 248 μmol ; TEAO at 149 μmol) and i.v. (TEA at a dose of 0.137 mmol; TEAO at 0.160 mmol). Following oral administration of TEA, diethylamine was detected in urine at a level $< 0.5\%$ of the administered dose. When TEAO was administered orally, the average urinary concentration was 10% of the administered dose. Diethylamine was not detected in the plasma following oral administration of TEAO. Following i.v. administration of TEA, diethylamine was not detected in urine samples, and only trace amounts were detected after administration of TEAO. The authors proposed that TEAO is metabolized to form diethylamine mainly within the gastrointestinal tract. They did note, however, that the levels of diethylamine formed following oral administration of TEA were low, and that diethylamine could not be found in the stomach, where formation of nitrosodiethylamine is most likely to occur (Åkesson et al., 1989).

9.2.1.2 Diethylamine as Metabolite of Disulfiram

In a study conducted by Faiman et al. (1984), the disposition of disulfiram and some of its metabolites (including diethylamine) were evaluated in 15 otherwise healthy male alcoholic patients. A single 250 mg dose of disulfiram was administered orally. The dose was repeated daily on days 4-15. The approximate plasma peak concentration of diethylamine 8-10 hours after the single 250 mg dose was 1.2 $\mu\text{g}/\text{mL}$ (16 mmol/mL), and after multiple 250 mg doses was 2.2 μg diethylamine/mL (30 $\mu\text{mol}/\text{mL}$). The half-life ($t_{1/2}$) of diethylamine in plasma was 13.9 ± 3.7 hours. In urine, diethylamine accounted for $1.6 \pm 0.8\%$ of the single administered dose of disulfiram, and $5.7 \pm 1.6\%$ of the repeated doses.

The urinary excretion of diethylamine following administration by gavage of the drug disulfiram to male Sprague-Dawley rats was investigated (Neiderhise and Fuller, 1980). Rats

were given either a single 50 mg dose of ^{14}C -disulfiram, or were pretreated with unlabeled disulfiram for 21 days, and then dosed with 50 mg ^{14}C -disulfiram. In rats given the single dose of disulfiram, the urinary excretion of diethylamine increased over time.

9.2.1.3 Nitrosation

The reaction of dietary amines with salivary nitrite may produce nitrosamines, which are potential carcinogens (Mirvish, 1975; cited by Tricker et al., 1992). Sander (1967; cited by Galea et al., 1975) and Sander et al. (1968) demonstrated that *in vivo* and *in vitro* nitrosation of amines is possible at pH 2-3. Weakly basic, secondary amines are easily nitrosated, but diethylamine is never nitrosated under these conditions. Other studies have shown that nitrosation of diethylamine is dependent on nitrite concentration (Preda et al., 1971; Galea et al., 1972; Galea and Preda, 1973; all cited by Galea et al., 1975). Galea et al. (1975) investigated the possibility of the *in vivo* formation of nitrosodiethylamine (diethylnitrosamine; DEN). Wistar rats (sex not provided) were administered 15 mg (220 μmol) sodium nitrite and 15 mg (200 μmol) diethylamine in the diet daily for up to 217 days. The diet contained 0.06% or 600 ppm diethylamine. At the end of the study, chromatographic analysis did not detect the presence of DEN in the stomachs of the dosed rats. DEN also was not detected in blood or milk of goats fed fresh kale containing 3% potassium nitrate for 3 days, followed by administration of a single oral dose of 200 mg/kg (1.8 mmol/kg) diethylamine hydrochloride in aqueous solution (Juskiewicz and Kowalski, 1976).

9.2.2 Acute Exposures

LD_{50} data are presented in **Table 3** for diethylamine and in **Table 4** for diethylamine hydrochloride; other acute exposure data are summarized in **Table 5** for diethylamine and **Table 6** for diethylamine hydrochloride.

Table 3. LD₅₀ Values for Diethylamine

Route	Species (Sex and Strain)	LD ₅₀	Reference
oral	mouse (sex and strain n.p.)	649 mg/kg (8.9 mmol/kg)	Eastman Kodak (1980; cited by Beard and Noe, 1981)
	mouse (sex and strain n.p.)	500-650 mg/kg (6.8-8.9 mmol/kg)	Kagan (1965); Patel et al. (1985; both cited by BIBRA, 1997)
	rat (male, Sherman albino)	540 mg/kg (7.4 mmol/kg)	Union Carbide (1950)
	rat (male Wistar)	1.41 mL/kg (1030 mg/kg; 14.1 mmol/kg)	Union Carbide (1979)
inhalation	rat (sex and strain n.p.)	5700 ppm (17000 mg/m ³ ; 230 mmol/m ³)	Union Carbide (1979)
	rat (sex and strain n.p.)	12000 mg/m ³ (3950 ppm; 164 mmol/m ³)	Smyth et al. (1951; cited by BIBRA, 1997)
dermal	rabbit (male, New Zealand White)	820 mg/kg (11 mmol/kg)	Union Carbide (1950)
	rabbit (male, New Zealand White)	0.89 mL/kg (630 mg/kg; 8.6 mmol/kg)	Union Carbide (1979)
i.p.	mouse (sex and strain n.p.)	585 mg/kg (8.00 mmol/kg)	Anon. (1977; cited by BIBRA, 1997)
	rat (sex and strain n.p.)	50 mg/kg (0.68 mmol/kg)	Henschler (1984; cited by BASF, 1995)

^a 4-hour exposure Abbreviations: i.p. = intraperitoneal; n.p. = not provided

Table 4. LD₅₀ Values for Diethylamine hydrochloride

Route	Species (Sex and Strain)	LD ₅₀	Reference
oral	mouse (sex and strain n.p.)	4860 mg/kg (44.3 mmol/kg)	Labor Hyg. Occup. Dis., (1957; cited by RTECS, 1996)
	mouse (albino, sex n.p.)	7700 mg/kg (70 mmol/kg)	Saratikov et al. (1984)
	rat (albino, sex n.p.)	9900 mg/kg (90 mmol/kg)	Saratikov et al. (1984)
	guinea pig (sex and strain n.p.)	9500 mg/kg (87 mmol/kg)	Saratikov et al. (1984)
s.c.	mouse (sex and strain n.p.)	1130 mg/kg (10.3 mmol/kg)	Heymans Inst. Pharmacol. (1957; cited by RTECS, 1996)
i.p.	mouse (sex and strain n.p.)	960 mg/kg (8.8 mmol/kg)	Japanese J. Pharmacol. (1951; cited by RTECS, 1996)

Route	Species (Sex and Strain)	LD ₅₀	Reference
i.v.	mouse (sex and strain n.p.)	320 mg/kg (2.9 mmol/kg)	Heymans Inst. Pharmacol. (1957; cited by RTECS, 1996)

Abbreviations: i.p. = intraperitoneal; i.v. = intravenous; n.p. = not provided; s.c. = subcutaneous

Table 5 Acute Toxicity of Diethylamine

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
<i>9.2.2.1 Oral Exposure</i>						
rat (Sherman albino; age n.p.)	exposed: 5 M per dose controls: none	diethylamine , purity n.p.	252, 500, 1000, or 2000 mg/kg (3.44-27.3 mmol/kg) by gavage in an aqueous solution	single dose; up to 21 days	The lowest dose was not lethal. Three of 5 rats administered 500 mg/kg (6.8-mmol/kg) died; death occurred on days 4, 6, and 8. Four of 5 rats administered 1000 mg/kg (13.7-mmol/kg) died; death occurred on days 1, 5 (2 rats), and 11. All rats administered 2000 mg/kg (27.3-mmol/kg) died; death occurred on day 0 (1 rat) and day 1 (4 rats). Rats administered 1000 or 2000 mg/kg (13.7 or 27.3 mmol/kg) were sluggish and had reduced body temperature, as indicated by roughening of the coat. Necropsy revealed congestion of lungs, liver, and kidneys; hemorrhage or necrosis of stomach; and congestion, hemorrhage, or opacity of intestine.	Union Carbide (1950)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rat (Wistar; 3- to 4-wk-old)	exposed: 5 M per dose controls: none	diethylamine, purity n.p.	0.25, 0.5, or 1.0 mL/kg (2.5, 5.0, or 10.0 mmol/kg) undiluted diethylamine by gavage	single dose; length of observation period n.p.	All MD and HD rats, and 4/5 LD rats died within 3 days. In rats that died, necropsy revealed lungs with petichiae (microscopic hemorrhagic spots); distended, red, ulcerated stomach that had thickened walls and adhered to surrounding tissue; yellow or red, gas-filled intestines; slightly dark kidneys; enlarged adrenals; and mottled liver, spleen, and kidneys. In rats that survived, mottled liver and thickened stomach wall were observed. The authors proposed that the delayed deaths following administration of undiluted diethylamine indicated potential cumulative toxicity.	Union Carbide (1979)
9.2.2.2 Inhalation Exposure						
mouse (OF ₁ ; age n.p.)	exposed: 6 M per dose controls: n.p.	diethylamine, purity n.p.	60-600 ppm (180-1800 mg/m ³ ; 2.5-25 mmol/m ³)	15 min. oronasal exposure; length of observation period n.p.	The onset of action was about 30 seconds to 1 minute, and the recovery of respiratory frequencies following exposure to the pre-exposure values was about 1 minute. The calculated concentration resulting in a 50% decrease in the respiratory rate (RD ₅₀) was 202 ppm (614 mg/m ³)	Gagnaire et al. (1989)
mouse (strain and age n.p.)	M (number n.p.)	diethylamine, purity n.p.	n.p.	30 min. exposure (head only)	The concentration causing a 50% decrease in the respiratory rate was 184 ppm (559 mg/m ³ ; 7.5 mmol/m ³).	Nielson and Yamigiwa (1989; cited by BIBRA, 1997)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rat (strain and age n.p.)	exposed: 6 per dose (sex n.p.) controls: none	diethylamine, purity n.p.	1000, 2000, 4000, or 8000 ppm (3000-24,000 mg/m ³ ; 40-330 mmol/m ³), or saturated vapor	4 h; 6 days	One of 6 rats died after exposure to 2000 ppm (6000 mg/m ³ ; 81.80 mmol/m ³) and 3/6 rats died with exposure to 4000 ppm (12000mg/m ³ ; 163.6 mmol/m ³). All rats exposed to 8000 ppm (24000 mg/m ³ ; 327.2 mmol/m ³) died within 3 h. With exposure to the saturated vapor, 4/6 rats died within 3.75 min. and 2/6 died within 24 h. Mortality in rats exposed to 1000 ppm (3000 mg/m ³ ; 40.90 mmol/m ³) was not given. Rats exposed to 4000 ppm (12000 mg/m ³ ; 163.6 mmol/m ³) exhibited irritation in the eyes and nostrils within an hour of dosing, and had tremors and poor coordination at the end of dosing. Exposure to 8000 ppm (24000 mg/m ³ ; 327.2 mmol/m ³) caused convulsions, bloody discharge from the nostrils, and severe irritation to the ears and feet. Exposure to saturated vapor caused extreme congestion of lungs, liver, kidneys, and spleen, as well as convulsions, loud rales, and corneal opacity.	Union Carbide (1950)
rat (strain and age n.p.)	exposed: 6 (sex n.p.) controls: n.p.	diethylamine, purity n.p.	4000 ppm (12,000 mg/m ³ ; 160 mmol/m ³) or saturated vapor	4 h; length of observation period n.p.	At 4000 ppm dose, 3/6 rats died. With exposure to saturated vapor, all rats died after 5 min.	Smyth et al. (1951; cited by Beard and Noe, 1981)
rat (strain and age n.p.)	exposed: 6 per dose (sex n.p.) controls: none	diethylamine, purity n.p.	4000 or 8000 ppm (12,000 or 24,000 mg/m ³ ; 160 or 320 mmol/m ³)	4 h; length of observation period n.p.	The LD was not lethal. All rats administered the HD died. Rats administered the LD had wet noses, partly closed eyes, and slight loss of coordination. Rats administered the HD exhibited gasping, nasal irritation, poor coordination, and bloody nasal discharge. In 1 HD rat, tonic convulsions were observed. No necropsy data were provided.	Union Carbide (1979)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.2.3 Dermal Exposure						
rabbit (strain and age n.p.)	exposed: 5 (sex n.p.) controls: none	diethylamine , purity n.p.	0.01 mL (0.10 mmol) undiluted diethylamine applied to belly	n.p.	Two rabbits exhibited marked erythema, 2 exhibited moderate erythema, and 1 had no reaction. Based on these results, diethylamine was classified as a grade 4 toxicant on a 10-grade scale (10 being most severe).	Union Carbide (1950)
rabbit (strain and age n.p.)	exposed: 5 per dose (sex n.p.) controls: none	diethylamine , purity n.p.	0.01 mL (0.10 mmol) undiluted diethylamine or 10% aqueous solution applied to clipped uncovered intact skin on belly	24 h; length of observation period n.p.	Administration of the undiluted dose produced moderate erythema in 2/5 rabbits, marked erythema in 1/6 rabbits, and moderate necrosis in 2/6 rabbits. The diluted dose was not irritating. On a 10-grade scale (10 being most severe), diethylamine was designated as a grade 6 irritant.	Union Carbide (1979)
rabbit (New Zealand White; age n.p.)	exposed: 5 M per dose controls: none	diethylamine , purity n.p.	250, 500, 1000, or 2000 mg/kg (3.44-27.3 mmol/kg) applied to occluded skin	24 h; 14 days	The lowest dose was not lethal. One of 5 rabbits administered 500 mg/kg (6.8-mmol/kg) died; death occurred on day 1. Three of 5 rabbits administered 1000 mg/kg (13.7-mmol/kg) died; death occurred on days 1 (2 rabbits) and 6 (1 rabbits). All rabbits administered 2000 mg/kg (27.3-mmol/kg) died on day 1. Hemorrhage and necrosis of the skin and underlying muscular layers were observed. Necropsy of animals that died revealed pale or mottled livers; pale, mottled, or roughened surfaces of the kidneys; and congested or hemorrhagic intestines. The spleen was darkened so that it was black, the pancreas was congested, and the testes were hemorrhagic.	Union Carbide (1950)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rabbit (New Zealand White; 3- to 5-month-old)	exposed: 4 M per dose controls: none	diethylamine, purity n.p.	0.5, 1.0 or 2.0 mL/kg undiluted (5, 10, or 20 mmol/kg), applied to intact occluded skin of trunk	24 h; length of observation period n.p.	One of 4 LD, 2/4 MD, and 4/4 HD rabbits died. MD rabbits died on days 1 and 4; HD rabbits all died on day 1. In LD rabbits, erythema or edema, and necrosis were observed. In MD rabbits, edema and necrosis were observed. In HD rabbits, necrosis was observed. In rabbits that died, mottled liver and dark renal medullae were observed. Gross examination of survivors revealed no remarkable effects.	Union Carbide (1979)
rabbit, young (strain n.p.)	6 (sex n.p.)	diethylamine, purity n.p.	0.5 mL (5.0 µM) applied to intact and shaven occluded skin	3 minutes of exposure; observed after 1, 4, and 24 h	Skin was discolored after 1 hour. After 24 hours, the skin was black and thickened; erythema and edema were observed.	ICI (1981; cited by BASF, 1995)
rabbit (New Zealand White; 10- to 11-wk-old)	exposed: 1 M controls: exposed rabbit served as own control	diethylamine, 100% pure	0.5 mL (5.0 mmol) undiluted diethylamine applied to intact occluded skin of dorsum	after 3 minutes of exposure, diethylamine was wiped off and skin was evaluated	There were signs of irritation, including severe erythema with sloughing of skin, after 3 minutes of exposure. When rated on a scale of 0-4 (4 being the most severe), the observed erythema scored 4. Due to the severe corrosiveness of the dose, the rabbit was euthanized.	Union Carbide (1986)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rabbit New Zealand White; young adult)	exposed: 3 (sex n.p.) controls: n.p.	diethylamine , purity n.p.	0.5 mL (5.0 mmol) undiluted diethylamine applied to intact occluded skin of right flank	after 3 minutes of exposure, diethylamine was wiped off and skin was evaluated; further evaluations were made at 1, 24, 48, and 72 h, and 7 days	Necrosis at the site of exposure was evident. The necrosis progressed to eschar (a thick crust) at 1 hour (2/3 rabbits) and 24 hours (3/3 rabbits). Eschar was observed throughout the 7-day observation period. A very slight edema was also detected during the observation period, but it diminished by the end of 7 days. On a scale of 0-4 (4 being the most severe), eschar scored 4 in 3/3 rabbits at all observation times between 1 and 7 days.	Hoechst Celanese Corp. (1989)
rabbit (albino; age n.p.)	exposed: 3 (sex n.p.) controls: n.p.	diethylamine , purity n.p.	0.5 mL (5.0 mmol) undiluted diethylamine applied to 1 intact and 1 abraded occluded skin site	24 h; 7 days	Diethylamine caused pain on abraded skin. Skin turned brown within 15 min. Twenty-four hours after initial exposure, large (3 cm) necrotic lesions were detected on all treated sites. These lesions became dry, hard, and concave within 48 hours, and later began to crack and peel.	Penwalt Corp. (1986)
9.2.2.4 Ocular Exposure						
rabbit (strain and age n.p.)	n.p.	diethylamine , purity n.p.	1% diethylamine in propylene glycol, applied in excess to eye	n.p.	The dose caused severe corneal damage. Diethylamine was classified as a grade-10 irritant on a 10-grade scale (10 being most severe).	Union Carbide (1950)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rabbit (strain and age n.p.)	exposed: 5 per dose (sex n.p.) controls: none	diethylamine , purity n.p.	0.005 mL undiluted diethylamine (50 µmol), or 0.5 mL of 1% or 5% aqueous solution	single application; 24 h	The undiluted dose and the 5% aqueous solution caused severe corneal injury. The 1% aqueous solution produced iritis. Diethylamine was classified as a grade-10 irritant on a 10-grade scale (10 being most severe).	Union Carbide (1979)
rabbit (albino; age n.p.)	exposed: 3 (sex n.p.) controls: none	diethylamine , purity n.p.	0.1 mL undiluted diethylamine (0.1 mmol) applied to conjunctival sac of both eyes; 1 eye of each rabbit was washed continuously with water 15 sec.-1 min. post-exposure (the other eye was not washed)	single application; 7 days	There was no difference in reaction to diethylamine in washed and unwashed eyes. Immediately following application of diethylamine, the cornea began to opacify. Opacification was virtually complete within 10 minutes post-exposure. Severe conjunctival inflammation and necrosis in portions of the conjunctivae and along the borders of the eyelids occurred rapidly. The necrosis solidified within a day or 2. The effects persisted throughout the observation period and appeared to be irreversible.	Penwalt Corp. (1986)
9.2.2.5 Intraperitoneal Injection						
mouse (strain and age n.p.)	n.p.	diethylamine , purity n.p.	20-160 or 320 mg/kg (0.3-2.2 or 4.4 mmol/kg)	n.p.	The high dose demonstrated curare-like and sedative activity and acted as a central nervous system depressant. The lower doses did not demonstrate diuretic, curare-like, or sedative activity in the mice.	Union Carbide (1954)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
mouse (strain and age n.p.)	n.p.	diethylamine, purity n.p.	32 mg/kg (0.44 mmol/kg)	single dose; observation period n.p.	Induced central nervous system depression.	Patel et al. (1985; cited by BIBRA, 1997)
rat (Cox; age n.p.)	exposed: 72 M controls: n.p.	diethylamine, purity n.p.	250, 500, or 1000 mg/kg (3.4, 7.0, or 14.0 mmol/kg)	single dose; 4 rats from each dose group were killed immediately after dosing, or 2, 6, 12, 24, or 48 hours after dosing	The LD produced minimal changes in the liver, including dilated sinusoids, at 2 h. At 6 hours, the changes included mild degeneration with disruption of lobular pattern. Twelve hours after administration of the LD, no changes were detected in the liver. With the MD, mild degeneration of the liver with disruption of lobular pattern occurred 2 h post-exposure, and marked liver degeneration with periportal necrosis and hydropic degeneration was evident 6 h post-exposure. By 12 h post-exposure, effects of the MD on the liver had diminished to minimal changes, and by 24 h post-exposure, there were no observable changes. The HD produced marked liver degeneration with periportal necrosis and hydropic degeneration at 2 h post-exposure. At 6 h post-exposure, liver changes became less severe, and by 48 h post-exposure, there were no observable changes in the liver. The concentration of serum ornithine carbamyl transferase (SOCT) was significantly increased in all dose groups. The concentration of serum aspartate aminotransferase (SAST) only became elevated with the MD and HD, and the concentration of serum alanine aminotransferase (SALA) only became elevated with the HD. By 24 hours post-exposure, all enzymes levels had returned to pre-exposure levels. SOCT, SAST, and SALA are indicators of hepatic injury.	Drotman and Lawhorn (1978)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Acute Toxicity of Diethylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rat (strain and age n.p.)	n.p.	diethylamine, purity n.p.	100 mg/kg (1.4 mmol/kg)	single dose; observation period n.p.	Treatment induced a reduction in the protein concentration in the liver.	Melnikova et al. (1985; cited by BIBRA, 1997)
guinea pig (strain and age n.p.)	n.p.	diethylamine, purity n.p.	50-500 mg/kg (0.7-7.0 mmol/kg)	n.p.	At a dose of 200-500 mg/kg (3.0-7.0 mmol/kg), diethylamine acted as a central nervous system depressant.	Union Carbide (1954)
9.2.2.6 Intravenous Injection						
dog (strain and age n.p.)	n.p.	diethylamine, purity n.p.	10-200 mg/kg (0.1-3.0 mmol/kg)	n.p.	Diethylamine induced gastrointestinal spasms, a drop in blood pressure, an increase in heart rate, a decrease in the force of cardiac beat, and a decrease in respiratory volume. Diethylamine also demonstrated parasympathomimetic, sympatholytic, cardiotoxic, and vasodilator activity in the dogs. At doses of 100-200 mg/kg (1.0-3.0 mmol/kg), diethylamine acted as a central nervous system and respiratory depressant in the dogs. The 200 mg/kg (3.0 mmol/kg) dose was lethal.	Union Carbide (1954)

Abbreviations: F = female; HD = high dose; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 6. Acute Toxicity of Diethylamine Hydrochloride

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
<i>9.2.2.1 Oral Exposure</i>						
mouse (albino; age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	n.p.	n.p.	Some animals exhibited ptosis (drooping of eyelids) and alteration of motor coordination and an increase of diuresis. No gross lesions were observed at necropsy.	Saratikov et al. (1984)
rat (albino; age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	n.p.	n.p.	Some animals exhibited ptosis (drooping of eyelids) and alteration of motor coordination and an increase of diuresis. No gross lesions were observed at necropsy.	
rat (albino; age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	40, 200, or 1000 mg/kg (0.4, 2, or 9 mmol/kg)	n.p.	Diethylamine hydrochloride behaved like a polytropic poison, disturbing chiefly the CNS and parenchymal organs. The threshold dose was 40 mg/kg (0.4 mmol/kg).	
guinea pig (strain and age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	n.p.	n.p.	Some animals exhibited ptosis (drooping of eyelids) and alteration of motor coordination and an increase of diuresis. No gross lesions were observed at necropsy.	

9.2.2.5 Intraperitoneal Injection						
mouse (strain and age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	200-300 or 500 mg/kg (2-3 or 5 mmol/kg)	single dose; observation period n.p.	The LD and MD caused the hair to stand on end. The HD induced tremors and an increase in the respiration rate.	Kase et al. (1967; cited by BIBRA, 1997)
9.2.2.6 Intravenous Injection						
dog (strain and age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	50 mg/kg (0.5 mmol/kg)	single dose; observation period n.p.	Induced an increase in respiration rate.	Kase et al. (1967; cited by BIBRA, 1997)

Abbreviations: HD = high dose; LD = low dose; MD = mid dose; n.p. = not provided

9.2.2.1 Oral Exposure

Severe toxicity leading to death occurred in Sherman albino rats administered a single dose of 500, 1000, or 2000 mg/kg (7, 14, or 27 mmol/kg) diethylamine by gavage (Union Carbide, 1950), and in Wistar rats administered a single dose of 0.25, 0.5, or 1.0 mL/kg (2.5, 5.0, or 10.0 mmol/kg) undiluted diethylamine (Union Carbide, 1979). Rats administered 1000 or 2000 mg/kg (13.7 or 27.3 mmol/kg) were sluggish and had reduced body temperature, as indicated by roughening of the coat. Necropsy revealed congestion of lungs, liver, and kidneys; hemorrhage or necrosis of stomach; and congestion, hemorrhage, or opacity of intestine. Administration of a single dose of 252 mg/kg (3.44 mmol/kg) diethylamine by gavage to Sherman albino rats was not lethal (Union Carbide, 1950).

In albino mice, albino rats, and guinea pigs administered diethylamine hydrochloride (dose not provided), intoxication was clinically characterized by a lowering of motor activity and excitability (Saratikov et al., 1984). No gross lesions were observed at necropsy. In albino rats, oral administration of 1/250, 1/50, or 1/10 the LD₅₀ (40-1000 mg/kg; 0.4-9 mmol/kg) produced changes in central nervous system (CNS) and parenchymal organs, with a threshold dose of 40 mg/kg (0.4 mmol/kg).

9.2.2.2 Inhalation Exposure

The expiratory bradypnea indicative of upper airway irritation in six male OF₁ mice was evaluated during a 15-minute oronasal exposure to 60-600 ppm (180-1800 mg/m³; 2.5-25 mmol/m³) diethylamine (Gagnaire et al., 1989). The onset of action was about 30 seconds to 1 minute, and the recovery of respiratory frequencies to pre-exposure levels was about 1 minute. The calculated concentration resulting in a 50% decrease in the respiratory rate (RD₅₀) was 202 ppm (614 mg/m³). In another study, the RD₅₀ for a 30-minute exposure was 550 mg/m³ (180

ppm; 7.5 mmol/m³) in male mice (strain not provided) (Nielson and Yamikiwa, 1989; cited by BIBRA, 1997).

Rats (sex and strain not given) were exposed to 1000, 2000, 4000, 8000 ppm (3000, 6000, 12000, 24000 mg/m³; 40-330 mmol/m³) or saturated diethylamine vapor for 4 hours. One of 6 rats died after exposure to 2000 ppm (6000 mg/m³; 81.80 mmol/m³) and 3/6 rats died with exposure to 4000 ppm (12000 mg/m³; 163.6 mmol/m³). All rats exposed to 8000 ppm (24000 mg/m³; 327.2 mmol/m³) died within 3 hours. Exposure to the saturated vapor caused 4/6 rats to die within 3.75 minutes and 2/6 within 24 hours. Mortality in rats exposed to 1000 ppm (3000 mg/m³; 40.90 mmol/m³) did not occur within a 6-day observation period (Union Carbide, 1950). Clinical observations of the rats exposed to 4000 ppm (12000 mg/m³; 163.6 mmol/m³) revealed irritation in the eyes and nostrils within an hour of dosing, and tremors and poor coordination at the end of the 4-hour dosing. Exposure to 8000 ppm (24000 mg/m³; 327.2 mmol/m³) caused convulsions, bloody discharge from the nostrils, and severe irritation to the ears and feet. Exposure to saturated vapor caused extreme congestion of lungs, liver, kidneys, and spleen, as well as convulsions, loud rales, and corneal opacity (Union Carbide, 1950).

Rats (strain and age not provided) were exposed to 4000 ppm (12000 mg/m³; 160 mmol/m³) diethylamine, or to saturated vapor for 4 hours (Smyth et al., 1951; cited by Beard and Noe, 1981). Three of 6 rats died with administration of the 4000 ppm (12000 mg/m³; 160 mmol/m³) dose. With exposure to saturated vapor, all rats died after 5 minutes.

In rats (strain and age not provided) exposed to 4000 or 8000 ppm (12000 or 24000 mg/m³; 80 or 160 mmol/m³) diethylamine for 4 hours, all rats administered the higher dose died after exhibiting gasping, nasal irritation, poor coordination, and bloody nasal discharge (Union Carbide, 1979). The lower dose was not lethal, but exposed rats exhibited wet noses, partly closed eyes, and slight loss of coordination.

9.2.2.3 Dermal Exposure

Moderate to marked erythema was detected on the belly after application of 0.01 mL (0.1 mmol) undiluted diethylamine to the skin of New Zealand White rabbits for 24 hours.

Diethylamine was classified as a grade 4 toxicant on a 10 grade scale (Union Carbide, 1950). The study was repeated, with similar findings but a reclassification of diethylamine as a grade 6 irritant (Union Carbide, 1979).

Severe toxicity leading to death occurred in New Zealand White rabbits that had 500, 1000, or 2000 mg/kg diethylamine (Union Carbide, 1950), or 0.5-2.0 mL/kg diethylamine (Union Carbide, 1979) applied to occluded skin for 24 hours. Toxic signs included hemorrhage and necrosis of the skin and underlying muscular layers, while necropsy of animals that died revealed pale or mottled livers; pale, mottled, or roughened surfaces of the kidneys; and congested or hemorrhagic intestines. Application of 250 mg/kg diethylamine to skin of New Zealand White rabbits was not lethal (Union Carbide, 1950).

Discoloration of the skin was observed one hour after a 3-minute-application of 0.5 mL (5.0 mmol) diethylamine to the skin of rabbits (strain n.p.) (ICI, 1981; cited by BASF, 1995). After 24 hours, the skin was black and thickened, and erythema and edema were observed. Severe skin irritation was present 3 minutes after application of 0.5 mL (5.0 mmol) undiluted diethylamine to the skin of New Zealand White rabbits (Union Carbide, 1986; Hoechst Celanese Corp., 1989). When rated on a scale of 0-4 (4 being most severe), the observed erythema scored 4 (Union Carbide, 1986). In another study (Hoechst Celanese Corp., 1989), at 3 minutes post-exposure, necrosis at the site of exposure was evident. The necrosis progressed to eschar (a thick crust) within 24 hours. Eschar was observed throughout the remaining 7-day observation period. On a scale of 0-4 (4 being the most severe), eschar scored 4.

In albino rabbits that had 0.5 mL (5.0 mmol) undiluted diethylamine applied to one intact and one abraded (hair was clipped) occluded skin site for 24 hours, diethylamine caused pain on

the abraded skin only (Pennwalt Corp., 1986). Treated skin turned brown within 15 minutes. Twenty-four hours after the initial exposure, large (3 cm) necrotic lesions were detected on all treated sites. These lesions became dry, hard, and concave within 48 hours, and later began to crack and peel.

9.2.2.4 Ocular Exposure

Severe corneal damage occurred in the eyes of rabbits following ocular application of 1% diethylamine solution in propylene glycol; 0.005 mL (50 μ mol) undiluted diethylamine; or 0.5 mL of a 5% aqueous solution (Union Carbide, 1950; 1979). Diethylamine was classified as a grade 10 irritant on a 10-grade scale. Application of a 1% aqueous solution caused iritis (inflammation of the iris, manifested by vascular congestion) (Union Carbide, 1979).

Severe ocular irritation occurred in albino rabbits after application of 0.1 mL (1 mmol) undiluted diethylamine to the conjunctival sacs of both eyes (Pennwalt Corp., 1986). The effects persisted throughout the 7-day observation period.

9.2.2.5 Intraperitoneal Injection

In mice (strain and age not provided), intraperitoneal (i.p.) injection of 320 mg/kg (4.4 mmol/kg) diethylamine caused curare-like response (paralysis of skeletal muscles), sedation, and central nervous system depression (Union Carbide, 1954). Injection of lower doses (20-160 mg/kg [0.3-2.2 mmol/kg]) of diethylamine in mice did not cause these effects. In another study, 32 mg/kg (0.44 mmol/kg) administered i.p. induced central nervous system depression in mice (strain and age not provided) (Patel et al., 1985; cited by BIBRA, 1997).

In Cox rats, diethylamine administered i.p. at doses ranging from 250 mg/kg to 1000 mg/kg (3.4-14.0 mmol/kg) caused temporary liver damage (Drotman and Lawhorn, 1978). A single

diethylamine dose of 100 mg/kg (1.4 mmol/kg) induced a reduction in the protein concentration in the liver of rats (strain and age not provided) (Melnikova et al., 1985; cited by BIBRA, 1997).

Guinea pigs were administered diethylamine by i.p. injection at doses of 50 to 500 mg/kg (0.7-7.0 mmol/kg). At doses of 200-500 mg/kg (3.0-7.0 mmol/kg), diethylamine acted as a central nervous system depressant (Union Carbide, 1954).

Diethylamine hydrochloride doses of 200 to 300 mg/kg (2-3 mmol/kg) induced piloerection in mice (strain and sex not provided) (Kase et al., 1967; cited by BIBRA, 1997). A 500 mg/kg dose (5 mmol/kg) induced tremors and an increase in the respiration rate.

9.2.2.6 Intravenous Injection

Diethylamine did not demonstrate anti-cholinesterase, antispasmodic, parasympatholytic, sympathomimetic, ganglionic-blocking, or diuretic activity in dogs (strain and age not provided) at i.v. doses of 10-200 mg/kg (0.1-3.0 mmol/kg) (Union Carbide, 1954). This dose range, however, did induce gastrointestinal spasms, a drop in blood pressure, an increase in heart rate, a decrease in the force of cardiac beat, and a decrease in respiratory volume. Diethylamine also demonstrated parasympathomimetic, sympatholytic, cardiotoxic, and vasodilator activity, and acted as a central nervous system and respiratory depressant. The highest dose was lethal due to respiratory failure quickly followed by cardiovascular collapse.

Diethylamine hydrochloride, at a dose of 50 mg/kg (0.46 mmol/kg), induced an increase in the respiration rate in dogs (strain and age not provided) (Kase et al., 1967; cited by BIBRA, 1997).

9.2.3 Short-term and Subchronic Exposures

Studies described in this section are summarized in **Table 7**.

Table 7. Short-term and Subchronic Toxicity

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
9.2.3.1 Oral Exposure						
rat (strain and age n.p.)	n.p.	diethylamine, purity n.p.	65 mg/kg/day (0.89 mmol/kg/day)	2.5 months	Growth retardation and increased amount of ascorbic acid in the liver were observed. Some animals died toward the end of the experiment. The results were not quantitatively evaluated.	Kagan (1965; cited by BASF, 1995)
rat (albino; age n.p.)	n.p.	diethylamine hydrochloride, purity n.p.	3 mg/kg (30 µmol/kg)	45 days;	Significant inhibition in hepatic excretory function, an increase in daily urine output, and sporadic changes in the summation threshold index and RBC and WBC counts.	Saratikov et al. (1984)
9.2.3.2 Inhalation Exposure						
mouse (B6C3F1; 32-40 days old)	exposed: 5 M, 5 F per dose controls: 10 M, 10 F	diethylamine, purity n.p.	250 or 1000 ppm (760 or 3000 mg/m ³ ; 10 or 14 mmol/m ³)	Exposed for 6 hours/day, 5 days/week over 15-16 days	One F exposed to 1000 ppm died on exposure day 1. All other mice at both dose levels had treatment-related lesions of the nasal cavity. The lesions consisted of acute ulcerative necrotizing rhinitis, squamous metaplasia of the nasal mucosa, and in some animals, turbinate atrophy. The 1000 ppm exposure level also induced the following effects: squamous metaplasia of the tracheal mucosa (3/5 M and 3/5 F); squamous metaplasia of the mainstem bronchial mucosa (2/5 M and 1/5 F). Cortical lymphoid depletion of the thymus and lymphoid depletion of the spleen observed in some of the animals exposed to 1000 ppm were noted as questionable treatment-related effects. No treatment-related or treatment-associated changes were observed in the heart, coronary arteries, or aorta.	Gorgacz (1987)

Abbreviations: F = female; M = male; n.p. = not provided

Table 7. Short-term and Subchronic Toxicity (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
rat (strain and age n.p.)	n.p.	diethylamine, purity n.p.	0.04, 0.4, or 4 mg/m ³ (0.01, 0.1, or 1 ppm; 0.00055, 0.0055, or 0.055 mmol/m ³)	Continuous exposure for 93 days	At the 4 mg/m ³ dose, chronaxy was altered after 8 weeks of exposure. At week 4, higher levels of the SH-group in the serum were observed. Increased coproporphyrin levels were observed throughout the entire length of the experiment. At the 0.4 mg/m ³ dose, similar effects were noted, but to a lesser degree. The 0.04 mg/m ³ dose group was not different from the control group. The test was not quantified due to a lack of data collected while performing the experiment and poor presentation of results.	Kosiborod (1968; cited by BASF, 1995)
rat (albino; sex n.p.)	n.p.	diethylamine, purity n.p.	0.37 or 4.19 mg/m ³ (0.12, 1.38 ppm; 5 or 57 µmol/m ³)	3 months	No adverse effects occurred with exposure to 0.05 mg/m ³ (0.7 µmol/m ³). Cerebral cortex changes (disruption of porphyrin metabolism and increased cholinesterase activity) occurred.	Tkachev (1969, 1971; cited by Franklin Research Center, 1979)
rat (strain and age n.p.)	n.p.	diethylamine, purity n.p.	0.07 or 0.14 mg/m ³ (0.02 or 0.046 ppm; 0.00096 or 0.0019 mmol/m ³)	Continuous exposure for 3 months	Changes were observed in the carbohydrate function of the liver, muscle chronaxy, and blood cholinesterase activity. No weight gain, changes in blood protein, or number of leukocytes and erythrocytes were observed. The authors noted a change in the function of the central nervous system and the liver. The study was only presented as a summary and effects were not quantified.	Tkachev and Kosiborod (1974; cited by BASF, 1995)
rat (Fischer 344; age n.p.)	exposed: 5 M, 5 F controls: 5 M, 5 F	diethylamine, purity n.p.	500 ppm (1500 mg/m ³ ; 20 mmol/m ³)	10 days ; observation period n.p.	Moderate to marked necrotizing inflammation of the nasal cavity was detected in all dosed rats.	Schueler (1984)

Abbreviations: F = female; M = male; n.p. = not provided

Table 7. Short-term and Subchronic Toxicity (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
rat (strain and age n.p.)	exposed: 5 M, 5 F controls: none	diethylamine, purity n.p.	500 ppm (1500 mg/m ³ ; 20 mmol/m ³)	10 days; observation period n.p.	Moderate to marked necrotizing inflammation of the nasal cavity was detected in all dosed rats. No other experimental details were given.	Virginia Chemicals (1984)
rat (F344; age n.p.)	exposed: 100 M, 100 F per dose controls: 100 M, 100 F	diethylamine, 99.9% pure	25 or 250 ppm (76 or 760 mg/m ³ ; 1.0 or 10 mmol/m ³), 5 days/week for 6.5 h/day	6 months; 10 M and 10 F sacrificed from each group after 30 and 60 days of exposure, 50 M and 50 F from each group sacrificed after 120 days of exposure, remaining rats not examined	Mean body weight was depressed in high dose rats. High dose rats also developed lesions of the nasal mucosa/respiratory epithelium, including squamous metaplasia, rhinitis, and lymphoid hyperplasia. There were no treatment-related effects in low dose rats. Cardiotoxicity was not observed in any group.	Lynch et al. (1986)
rat (F344; 40-49 days old)	exposed: 5 M, 5 F per dose controls: 10 M, 10 F	diethylamine, purity n.p.	250 or 1000 ppm (760 or 3000 mg/m ³ ; 10.2 or 13.7 mmol/m ³)	Exposed for 6 hours/day, 5 days/week over 15-16 days	All rats at both dose levels had treatment-related lesions of the nasal cavity. The lesions consisted of acute ulcerative necrotizing rhinitis, squamous metaplasia of the nasal mucosa, and in some animals, turbinate atrophy. The 1000 ppm exposure level also induced squamous metaplasia of the tracheal mucosa in 1/5 M. A treatment-associated lesion consisting of acute suppurative peribronchiola was observed in most lung lobes of several 1000 ppm treated rats and one 250 ppm treated rat. Congestion in the tracheobronchial lymph nodes and thymic involution observed in some rats were noted as questionable treatment-related or treatment-associated effects. No treatment-related or treatment-associated changes were observed in the heart, coronary arteries, or aorta.	Gorgacz (1987)

Abbreviations: F = female; M = male; n.p. = not provided

Table 7. Short-term and Subchronic Toxicity (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
rabbit (strain and age n.p.)	n.p.	diethylamine, purity n.p.	50 or 100 ppm (150 or 300 mg/m ³ ; 200 or 400 mmol/m ³), 5 days/week for 7 h/day	6 wk; observation period n.p.	No deaths occurred. Exposure to 50 ppm caused marked chronic irritation of the lungs. Exposure to 100 ppm produced parenchymatous degeneration and, occasionally, inflammatory processes in liver and kidneys.	Brieger and Hodes (1951)
rabbit (strain and age n.p.)	n.p.	diethylamine, purity n.p.	50 ppm (150 mg/m ³ ; 200 mmol/m ³)	2 wk; observation period n.p.	In this review, it was noted that corneal erosion developed 2 weeks post-exposure. The rabbits also exhibited conjunctival and pulmonary irritation.	Grant (1974; cited by NIOSH/ OSHA, 1981)

9.2.3.3 Potentially Nitrosated Diethylamine

rat (strain and age n.p.)	exposed: 16 (sex n.p.) controls: n.p.	diethylamine, purity n.p.	0.3% diethylamine and 0.3% sodium nitrite in standard diet	8 rats were killed after 6 mo	No rats died during exposure and no pathological changes were noted. No other details were given.	Sander et al. (1968)
rat (Wistar; age n.p.)	exposed: 25 (sex n.p.) controls: 25 (sex n.p.; fed basal diet alone)	diethylamine, purity n.p.	15 mg (220 µmol) sodium nitrite and 15 mg (200 µmol) diethylamine in diet daily (diet contained 0.06% of each compound)	217 days (~ 7 mo); 3 rats from each group were sacrificed every 30 days	Hyperplasia of Kupffer cells, and small inflammatory infiltrates in the portal areas, as well as chronic interstitial nephritis were detected in dosed rats (incidences not given). Chromatographic analysis did not detect nitrosodiethylamine in the stomachs of dosed rats.	Galea et al. (1975)

Abbreviations: F = female; M = male; n.p. = not provided

9.2.3.1 Oral Exposure

When rats (strain not provided) were administered diethylamine orally at 65 mg/kg/day (0.89 mmol/kg/day) for 2.5 months, growth retardation and increased amounts of ascorbic acid in the liver were observed (Kagan, 1965; cited by BASF, 1995). Some animals died toward the end of the experiment. The results were not quantified.

In albino rats, oral administration of diethylamine hydrochloride at a dose of 3 mg/kg (30 μ mol/kg) for 45 days, produced a statistically significant inhibition in hepatic excretory function, an increase in daily urine output, and sporadic changes in the summation threshold index and RBC and WBC counts (Saratikov et al., 1984).

9.2.3.2 Inhalation Exposure

In a study by Gorgacz (1987), male and female B6C3F1 mice were exposed to 250 or 1000 ppm (760 or 3000 mg/m³; 10 or 14 mmol/ m³) for 6 hours per day, 5 days per week over 15 or 16 days. The treatment induced lesions of the nasal cavity in all surviving treated mice. The lesions consisted of acute ulcerative necrotizing rhinitis, squamous metaplasia of the nasal mucosa, and in some animals, turbinate atrophy. Other treatment-related effects induced in some mice exposed to the 1000 ppm exposure level included squamous metaplasia of the tracheal mucosa and squamous metaplasia of the mainstem bronchial mucosa. Although cortical lymphoid depletion of the thymus and lymphoid depletion of the spleen were observed in some animals exposed to 1000 ppm; the author stated that it was questionable whether these effects were related to treatment. No treatment-related or treatment-associated changes were observed in the heart, coronary arteries, or aorta.

In rats (sex and strain not provided) exposed by inhalation to 4 mg/m³ (1 ppm; 0.0055 mmol/m³) diethylamine for 93 days, muscle chronaxies were altered after 8 weeks of exposure (Kosiborod 1968; cited by BASF, 1995). Higher levels of the sulfhydryl (SH)-group were observed in the serum after 4 weeks, and an increase in coproporphyrin releases was observed over the entire

length of the experiment . At the 0.4 mg/m³ (0.1 ppm; 0.0055 mmol/m³) dose level, similar effects were observed, but to a lesser degree. The low dose group (0.04 mg/m³; 0.01 ppm; 0.00055 mmol/m³) was not different from the control. The test was not quantified due to a lack of data collected while performing the experiment and poor presentation of results.

Cerebral cortex changes (disruption of porphyrin metabolism and increased cholinesterase activity) were reported in albino rats exposed by inhalation to 0.37 or 4.19 mg/m³ (5 or 57 µmol/m³) diethylamine for 3 months. No adverse effects occurred with exposure to 0.05 mg/m³ (0.7 µmol/m³) (Tkachev, 1969, 1971; cited by Franklin Research Center, 1979).

Changes were observed in the carbohydrate function of the liver, muscle chronaxy, and blood cholinesterase activity when rats (sex and strain and age not provided) were exposed to 0.07 or 0.14 mg/m³ (0.02 or 0.046 ppm; 0.00096 or 0.0019 mmol/m³) diethylamine by inhalation for 3 months (Tkachev and Kosiborod, 1974; cited by BASF, 1995). The authors noted a change in the function of the central nervous system and liver. The study was presented as a summary and the observed effects were not quantified.

Male and female Fischer 344 rats (age not provided) exposed to 500 ppm (1500 mg/m³; 20 mmol/m³) diethylamine for 10 days demonstrated moderate to marked necrotizing inflammation of the nasal cavity (Schueler, 1984). The results were confirmed in a study by Virginia Chemicals (1984).

In male and female F344 rats (age not provided) exposed by inhalation to 25 or 250 ppm diethylamine 6.5 hours/day, 5 days/week for up to 6 months, high dose rats developed lesions of the nasal mucosa/respiratory epithelium, including squamous metaplasia, rhinitis, and lymphoid hyperplasia (Lynch et al., 1986). Mean body weight was also depressed in this group. There were no treatment-related effects in low dose rats. Cardiotoxicity was not observed in any group.

Exposure to 250 or 1000 ppm (760 or 3000 mg/m³; 10 or 14 mmol/ m³) for 6 hours per day, 5 days per week over 15 or 16 days induced lesions of the nasal cavity in all exposed male and

female F344 rats (Gorgacz, 1987). The lesions consisted of acute ulcerative necrotizing rhinitis, squamous metaplasia of the nasal mucosa, and in some animals, turbinate atrophy. The 1000 ppm exposure level also induced squamous metaplasia of the tracheal mucosa. A treatment-associated lesion consisting of acute suppurative peribronchiola was observed in most lung lobes of several 1000 ppm treated rats and one 250 ppm treated rat. Congestion in the tracheobronchial lymph nodes and thymic involution were observed in some rats, but it was questionable whether these effects were related to treatment. No treatment-related or treatment-associated changes were observed in the heart, coronary arteries, or aorta.

Rabbits (strain and age not provided) were exposed to 50 or 100 ppm (150 or 300 mg/m³) diethylamine for 7 hours/day, 5 days/week, for 6 weeks (Brieger and Hodes, 1951). No mortality occurred. Exposure to 50 ppm (150 mg/m³) caused marked chronic irritation of the lungs, while exposure to 100 ppm (300 mg/m³) also produced parenchymatous degeneration and, occasionally, inflammatory processes in the liver and the kidneys.

In rabbits (strain and age not provided), corneal erosion occurred after 2 weeks of exposure to 50 ppm (150 mg/m³) diethylamine (Grant, 1974; cited by NIOSH/OSHA, 1981). The rabbits also exhibited conjunctival and pulmonary irritation.

9.2.3.3 Potentially Nitrosated Diethylamine

No toxicity was observed in Sprague-Dawley rats fed a standard diet with addition of 0.3% (3000 ppm) diethylamine and 0.3% sodium nitrite for 6 months (Sander et al., 1968). Diethylamine was not administered alone to any rats.

Wistar rats (sex not provided) administered 15 mg (220 µmol) sodium nitrite and 15 mg (200 µmol) diethylamine in the diet daily for up to 217 days exhibited hyperplasia of Kupffer cells, and small inflammatory infiltrates in the portal areas, as well as chronic interstitial nephritis. Chromatographic analysis did not detect nitrosodiethylamine in the stomachs of the dosed rats (Galea et al., 1975). Diethylamine was not administered alone to any rats.

9.2.4 Chronic Exposures

No chronic exposure studies were located.

9.3 Reproductive Effects

9.3.1 Diethylamine

No studies were located on reproductive effects.

9.3.2 Potentially Nitrosated Diethylamine Hydrochloride

The study described in this section and summarized in **Table 8** was conducted to evaluate the potential for nitrosoated diethylamine to induce reproductive toxicity.

In a 3-generation chronic study, rats (strain not provided) were administered sodium nitrite (100 mg/kg; 1000 μ mol/kg) in drinking water beginning at 30 days of age (Druckrey et al., 1963). The F₁ and F₂ offspring of the rats administered sodium nitrite were then given either sodium nitrite (100 mg/kg in drinking water) and diethylamine hydrochloride (500 mg/kg [5000 μ mol/kg] in fresh ground meat) concurrently, or sodium nitrite alone (100 mg/kg in drinking water) for life. No treatment related effects were reported, and the average lifespan, reproduction and birth of pups were described as normal in all groups. Diethylamine hydrochloride was not administered as a single compound to any rats.

9.4 Carcinogenicity

Studies described in this section are summarized in **Table 9**.

Table 8. Reproductive Toxicity

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
rat (strain n.p.; 30-day-old)	exposed: 30 F ₁ and 37 F ₂ rats (sex n.p.) controls: 30 F ₀ , 30 F ₁ , 34 F ₂ rats (NaNO ₂ alone; sex n.p.)	diethylamine hydrochloride and NaNO ₂ , purity n.p.	F ₀ rats were administered NaNO ₂ (100 mg/kg; 1000 µmol/kg) in drinking water beginning at 30 days of age. F ₁ and F ₂ rats were then given either NaNO ₂ (100 mg/kg in drinking water) and diethylamine hydrochloride (500 mg/kg [5000 µmol/kg] in fresh ground meat) concurrently, or sodium nitrite alone (100 mg/kg in drinking water) for life	See Dose	No treatment related effects were reported, and the average lifespan, reproduction and birth of pups were described as normal in all groups. Diethylamine hydrochloride was not administered as a single compound to any rats.	Druckrey et al. (1963)

Table 9. Carcinogenicity

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
9.4.1 Diethylamine						
rabbit (strain and age n.p.)	n.p.	diethylamine, purity n.p.	50 or 100 ppm (150 or 300 mg/m ³), 7 hr/day by inhalation	16 wk.; length of observation period n.p.	No tumors induced.	HSDB (1996)
aquarium fish (<i>Danio rerio</i>)	n.p.	diethylamine, purity n.p.	fish were immersed in 1/6-1/4 of LD ₅₀ (actual doses n.p.)	n.p.	No tumors were detected.	Khudoley (1987a)

Abbreviations: F = female; M = male; n.p. = not provided

Table 9. Carcinogenicity (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
9.4.2 Potentially Nitrosated Diethylamine hydrochloride						
mouse (C ₅₇ BL x C ₃ H; 15-day-old)	exposed: 30-35 M (diethylamine hydrochloride + NaNO ₂) controls: 30-35 M (diethylamine hydrochloride alone); 30-35 M (NaNO ₂ alone); 30-35 M (distilled water alone)	diethylamine hydrochloride and NaNO ₂ , purity n.p.	50 mg/kg (0.46 mmol/kg) diethylamine hydrochloride 50 mg/kg (0.46 mmol/kg) diethylamine hydrochloride by gavage followed immediately by 50 mg/kg NaNO ₂ by gavage Other controls were gavaged with 50 mg/kg NaNO ₂ alone or 0.1 mL/g distilled water	single dose; 70-110 wk observation period	No significant increase in liver tumors in diethylamine hydrochloride-treated mice. Liver tumors were detected in 17/34 mice co-administered diethylamine hydrochloride and NaNO ₂ , in 5/15 mice administered diethylamine hydrochloride alone, in 3/11 mice administered NaNO ₂ alone, and in 2/17 mice administered distilled water alone. The increase in the incidence of liver tumors in the group of mice co-administered diethylamine hydrochloride and NaNO ₂ was statistically significant, as compared to the groups administered diethylamine hydrochloride alone, NaNO ₂ alone, and distilled water alone.. Hepatic lesions were first observed at 70 weeks in mice administered diethylamine hydrochloride and NaNO ₂ or diethylamine hydrochloride alone.	Rijhsinghani et al. (1982)
rat (strain n.p.; 30-day-old)	exposed: 30 F ₁ and 37 F ₂ rats (sex n.p.) controls: 30 F ₀ , 30 F ₁ , 34 F ₂ rats (NaNO ₂ alone; sex n.p.)	diethylamine hydrochloride and NaNO ₂ , purity n.p.	F ₀ rats were administered NaNO ₂ (100 mg/kg; 1000 µmol/kg) in drinking water beginning at 30 days of age. F ₁ and F ₂ rats were then given either NaNO ₂ (100 mg/kg in drinking water) and diethylamine hydrochloride (500 mg/kg [5000 µmol/kg] in fresh ground meat) concurrently, or sodium nitrite alone (100 mg/kg in drinking water) for life	For life	There was no significant increase in tumor incidence.	Druckrey et al. (1963)

Abbreviations: NaNO₂,= sodium nitrite; n.p. = not provided

Table 9. Carcinogenicity (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/Observation Period	Results/Comments	Reference
guinea pigs (English short-hair; 21- to 28-day-old)	<p>exposed: 20 M (low mix), 20 M (high mix)</p> <p>controls: 20 M (4.0 g/L [36 mM] diethylamine hydrochloride alone); 20 M (0.8 g/L NaNO₂ alone); 20 M (plain water)</p>	diethylamine hydrochloride and NaNO ₂ , purity n.p.	<p>low mix: 2.0 g/L (18 mM) diethylamine hydrochloride + 0.4 g/L (6 mM) NaNO₂ for 2.5 yr</p> <p>high mix: 4.0 g/L diethylamine hydrochloride (36 mM) + 0.8 g/L (10 mM) NaNO₂ for 18 months followed with plain water for 12 months</p>	2.5 yr	No liver tumors were detected in guinea pigs from any treatment group.	Sen et al. (1975)

Abbreviations: NaNO₂,= sodium nitrite; n.p. = not provided

9.4.1 Diethylamine

No tumors were induced in rabbits (strain and age not specified) exposed by inhalation to 50 or 100 ppm (150 or 300 mg/m³) diethylamine for 7 hours/day for 16 weeks (HSDB, 1996). No other details were given.

No tumors were detected in aquarium fish (*Danio rerio*) immersed in water containing 1/6-1/4 of the LD₅₀ for diethylamine (actual doses and duration of exposure were not provided) (Khudoley, 1987a).

9.4.2 Potentially Nitrosated Diethylamine Hydrochloride

The incidence of liver tumors was not increased in 15-day-old male C₅₇BL x C₃H mice administered a single dose of 50 mg/kg (460 μmol/kg) diethylamine hydrochloride by gavage (Rijhsinghani et al., 1982). However, when treatment was followed immediately by doses with 50 mg/kg sodium nitrite (NaNO₂), there was a significant increase in liver tumors as compared to mice administered diethylamine hydrochloride alone, NaNO₂ alone, or distilled water alone). The mice were observed for up to 110 weeks after treatment.

There was no significant increase in tumor incidence in a 3-generation rat study in which diethylamine hydrochloride was administered concurrently with sodium nitrite (Druckrey et al., 1963). Rats (strain not provided) were administered sodium nitrite (100 mg/kg; 1.0 mmol/kg) in drinking water beginning at 30 days of age. The F₁ and F₂ offspring of the rats administered sodium nitrite were then given either sodium nitrite (100 mg/kg in drinking water) and diethylamine hydrochloride (500 mg/kg [5.0 mmol/kg] in fresh ground meat) concurrently, or sodium nitrite alone (100 mg/kg in drinking water) for life. Diethylamine hydrochloride was not administered alone to any rats.

No liver tumors were detected in male English short-hair guinea pigs (21- to 28-day-old) after oral (in drinking water) administration of 4.0 g/L (36 mM) diethylamine hydrochloride for

2.5 years or after concurrent administration of diethylamine hydrochloride and sodium nitrite. The guinea pigs that were administered both diethylamine hydrochloride and sodium nitrite received either a low mix consisting of 2.0 g/L (18 mM) diethylamine hydrochloride + 0.4 g/L (6 mM) sodium nitrite for 2.5 years, or a high mix consisting of 4.0 g/L diethylamine hydrochloride (36 mM) + 0.8 g/L (10 mM) sodium nitrite for 18 months, after which plain water was given for 12 months (Sen et al., 1975).

9.5 Genotoxicity

Studies described in this section are summarized in **Table 10**.

9.5.1 Prokaryotic Systems

Incubation with diethylamine (140 mg/L; 1900 mM) for 1 hour in the absence of metabolic activation did not induce lambda prophage in *Escherichia coli* strain K-12 (58-161 and C600) (Thomson and Woods, 1975).

Several studies have reported that diethylamine was not mutagenic in *Salmonella typhimurium*. Cotruvo et al. (1977) first concluded that neither diethylamine nor ozonated diethylamine induced gene mutations in *Salmonella typhimurium*. Strains TA98, TA100, TA1535, TA1536, TA1537, and TA1538 were exposed to 220 µmol/plate diethylamine in the absence and presence of rat liver S9. Diethylamine was ozonated in water for 1 hour at pH 11.1.

Ohe (1982; cited by BASF, 1995) reported that diethylamine hydrochloride at concentrations of 5 to 20 µmol/plate did not induce gene mutations in *S. typhimurium* strains TA98 or TA100 in the presence or absence of S9.

Zeiger et al. (1987) also concluded that diethylamine did not induce *his* gene mutations in *S. typhimurium*. Strains TA100, TA98, TA1535, and TA1537 were exposed to a dose range of 33 to 3333 µg/plate (0.5 to 46 µmol/plate) using the preincubation method in either the presence

or absence of 10% rat or hamster liver metabolic activation. No increase in the number of revertants was observed at any dose level in any strain under any S9 condition.

Similarly, diethylamine (dose levels not provided) did not induce *his* gene mutations in *S. typhimurium* strains TA100, TA98, and TA1538 using the plate incorporation method in either the presence or absence of rat liver S9 (Khudoley et al., 1987b).

However, a variety of biochemical mutants were induced by diethylamine in *Streptomyces scabies* (Ali et al., 1981). Bacteria were exposed to 0.05 and 0.1 mL diethylamine per 20 mL (34 and 68 $\mu\text{mol/mL}$) complete media for 4 days at 28°C in the absence of metabolic activation. Surviving colonies were isolated and retested for mutations on minimal media. Twenty amino acids requiring biochemical mutants were isolated at the low dose level. Biochemical mutants were not investigated for the high dose level.

Table 10. Genotoxicity

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.5.1 Prokaryotic Systems							
<i>Escherichia coli</i> strain K-12 (58-161 and C600)	lambda prophage induction	-	diethylamine, n.p.	140 mg/L; 1900 mM	negative	Incubation was for 3 hours in suspension culture.	Thomson and Woods. (1975)
<i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, TA1536, TA1537, and TA1538	<i>his</i> reverse gene mutations	-/+	diethylamine, n.p.	8040 ppm (220 µmol/plate) diethylamine was also ozonated in water for 1 hour at pH 11.1.	negative/negative	Neither diethylamine or ozonated diethylamine induced mutations. No other experimental details were given.	Cotruvo et al. (1977)
<i>S. typhimurium</i> strains TA98 and TA100	<i>his</i> reverse gene mutations	-/+	diethylamine hydrochloride, n.p.	5-20 µmol/plate	negative/negative		Ohe (1982; cited by BASF, 1995)
<i>S. typhimurium</i> strains TA100, TA98, TA1535, and TA1537	<i>his</i> reverse gene mutations	-/+ rat or hamster	diethylamine, n.p.	33, 100, 333, 1000, and 3333 µg/plate (0.5, 1.4, 4.6, 13.7, and 46 µmol/plate)	negative/negative	Pre-incubation method was used.	Zeiger et al. (1987)
<i>S. typhimurium</i> strains TA100, TA98, and TA1538	<i>his</i> reverse gene mutations	-/+	diethylamine, n.p.	n.p.	negative/negative	Plate incorporation method was used.	Khudoley et al. (1987b)
<i>Streptomyces scabies</i> (strain n.p.)	biochemical mutations	-	diethylamine, n.p.	0.05 and 0.1 mL per 20 mL (34 and 68 µmol/mL) complete media for 4 days at 28°C	positive	Twenty biochemical mutants were isolated from the low dose (histidine, adenine, arginine, tryptophan, methionine, leucine, or lysine requiring).	Ali et al. (1981)
9.5.2 Lower Eukaryotic Systems							
<i>Saccharomyces cerevisiae</i> strain D273-10B	petite mutants	-	n.p.	100 µmol/mL for 6 hr at 30°C in the presence of bubbling O ₂ or N ₂ .	negative		Mayer (1971)
<i>S. cerevisiae</i> strain D3	mitotic recombination	-	n.p.	100 mmol/mL for 6 hr at room temp. in the presence of bubbling O ₂ or N ₂ .	negative		Mayer (1973)

Abbreviations: n.p.=not provided

Table 10. Genotoxicity

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
<i>S. cerevisiae</i> strain D3	gene mutations (locus n.p.)	-/+	n.p.	8040 ppm (110 µmol/mL, exposure time n.p.). Diethylamine was also ozonated in water for 1 hour at pH 11.1.	negative/negative		Cotruvo et al. (1977)

Abbreviations: n.p.=not provided

Table 10. Genotoxicity (continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
<i>9.5.3 In Vivo Mammalian DNA Damage</i>							
rat (Fischer 344; male)	Unscheduled DNA synthesis (UDS)	n.p.	n.p.	500 mg/kg (6.84 mmol/kg) via gavage for 12 h	negative	Kidney cells were isolated 12 hours after exposure by <i>in situ</i> collagenase perfusion and incubated for 20 hours in the presence of [³ H]thymidine.	Loury et al. (1987)

Abbreviations: n.p.=not provided

9.5.2 Lower Eukaryotic Systems

Diethylamine induced neither petite mutants in the yeast *Saccharomyces cerevisiae* strain D273-10B (Mayer, 1971), nor mitotic recombination in strain D3 (Mayer, 1973), exposed in the absence of S9 to 100 $\mu\text{mol/mL}$ diethylamine for 6 hours, in the presence of either oxygen or nitrogen gas.

Neither diethylamine nor ozonated diethylamine induced gene mutations (type not provided) in *S. cerevisiae* (Cotruvo et al., 1977). Strain D3 was exposed to 8040 ppm (110 $\mu\text{mol/mL}$) diethylamine in the absence and presence of rat liver S9 (total exposure time not provided).

9.5.3 *In Vivo* Mammalian DNA Damage

Male Fischer 344 rats exposed via gavage to 500 mg/kg (6.84 mmol/kg) diethylamine and sampled 12 hours later did not exhibit unscheduled DNA synthesis (UDS) in their kidney cells (Loury et al., 1987).

9.6 Immunotoxicity

In guinea pigs, diethylamine, administered i.p. at a dose of 0.05-0.5 g/kg (0.7-7 mmol/kg), did not demonstrate antihistaminic activity (Union Carbide, 1954).

No immunotoxicity was observed in a two-stage sensitization test using female CF1 (BR) albino mice (6- to 8-week-old) (Virginia Chemicals, 1987). A 0.1 mL dose of a 1.0% diethylamine solution (v/v, in 70% ethanol) was applied to a clipped abdomen on days 0, 1, 2, and 3 of the study. On day 10, challenge was done by applying 0.01 mL of a 50% diethylamine solution (v/v, in 70% ethanol) to the dorsal and ventral surfaces of the left ear. Rechallenge was done on day 17 to the dorsal and ventral surfaces of the right ear. When mice were evaluated on study days 11, 12, 18, and 19 for changes in ear thickness of at least 20%, no changes were noted.

9.7 Other Toxic Effects

Diethylamine caused an inhibition of cerebral and hepatic monoamine oxidase (MAO) activity in albino rats injected i.p. with diethylamine (dose not provided) (Valiev, 1974).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Separate toxicological summaries on triethylamine and diallylamine have been prepared. Structure-activity relationships have not been reviewed.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL <http://www.gpo.ucop.edu/>

STN International Files

BIOSIS (Biological Abstracts)

EMBASE (Excerpta Medica)

HSDDB (Hazardous Substances Data Bank)

MEDLINE (Index Medicus)

RTECS (Registry of Toxic Effects of Chemical Substances)

TOXLINE

TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB

Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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